

# PRINCIPLES OF MEDICINAL CHEMISTRY REFINEMENT FOR CNS DRUG DISCOVERY

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# PRINCIPLES OF MEDICINAL CHEMISTRY REFINEMENT FOR CNS DRUG DISCOVERY

Three critical medicinal chemistry activities lead to drug candidates

1. Lead Identification
2. Lead Optimization
3. Chemical Preformulation

# LEAD IDENTIFICATION (1)

“The standard *modus operandi* of drug discovery is the identification of biologically active molecules *via* the **high throughput screening (HTS)** of large, diverse compound collections against specific biological targets, in low complexity assays systems.

The specific biological targets of interest are selected from the results of basic scientific research on the aetiology of the disease of interest.

Despite the *a priori* scientific appeal of the current standard approach, **the rise in its popularity has also been concurrent with a reported decline in the productivity of the pharmaceutical industry**, although of course this relationship is not necessarily causal and can be challenged.

**Additionally, the HTS approach has often over-shadowed a wider variety of alternative and complementary drug discovery strategies that have been very successfully employed in the discovery of new medicines.”**

(Hopkins, A. et al. *Ann. Rep. Med. Chem.* **2005**, 40, 339-348.)  **PRESTWICK CHEMICAL**  
A medicinal chemistry company

## LEAD IDENTIFICATION (2)

A retrospective analysis of the drug discovery routes highlights **five efficacious strategies** giving access to lead compounds:

- *Systematic screening*, often of large numbers of diverse compounds in biological assays (e.g. HTS)
- *Analogue design* modification of existing active molecules to create an improved medicine (or new intellectual property)
- *Serendipous observations* of unexpected clinical or pharmacological activities (trinitrine, hypoglycemic sulfonamides, sildenafil, etc.)
- *Rational design* of drugs resulting from the knowledge of the molecular mechanism and its role in disease (captopril, cimetidine)
- *Selective optimization of side activities* of known drugs on new pharmacological targets (SOSA Approach)

# LEAD OPTIMIZATION

Lead optimization deals with the structure-activity relationships (SAR's), it involves all the skills, the know-how and the expertise of the medicinal chemists. Often it constitutes the bottleneck of a research program.

Molecular modeling represents a valuable accompanying tool.

*1 - Molecular modifications*

*2 - The usefulness of modeling*

# *Possible modifications: "food for thoughts"*

Synthesis of:

Homologues, Vinylogues, Benzologues, Isosteres

Exploration of:

Positional isomers, Geometrical isomers

Optical isomers

Ring Modifications:

Opening, Closure, Ring extension

Ring contraction, Conformational restriction

Explaining the role of substituents:

Electronic, steric and lipophilic properties,

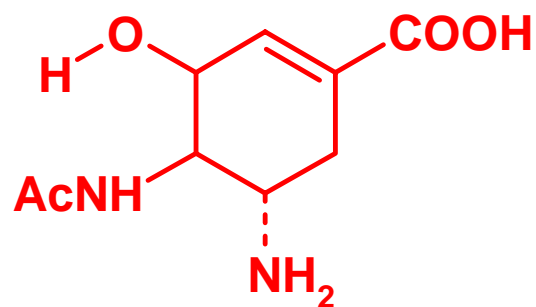
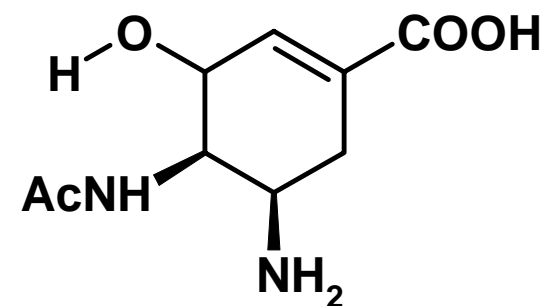
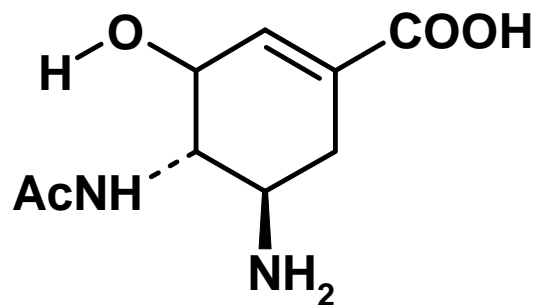
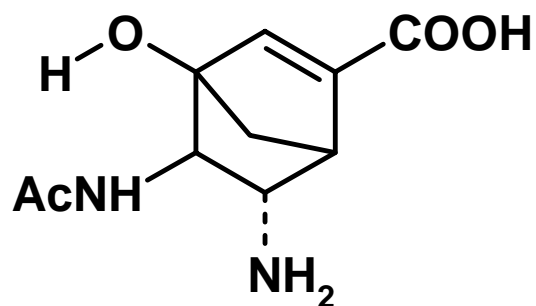
Metabolism

Preparing Twin Drugs

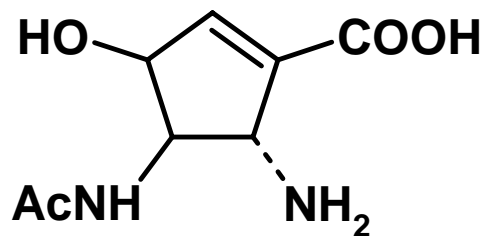
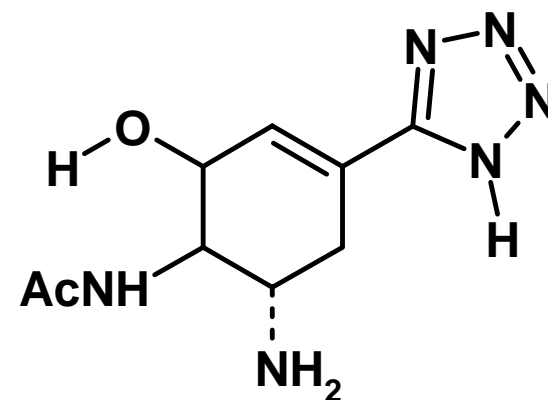
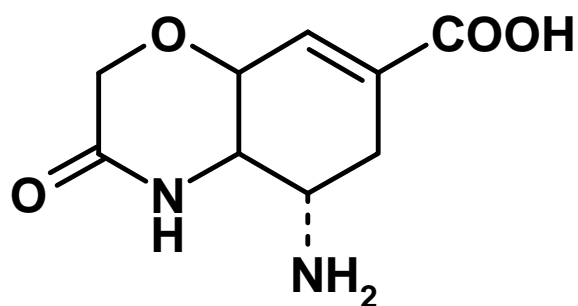
Identical twin drugs, Non-identical twin drugs

# Synthesis of homologues (1)

Optimisation: an organic chemist's view

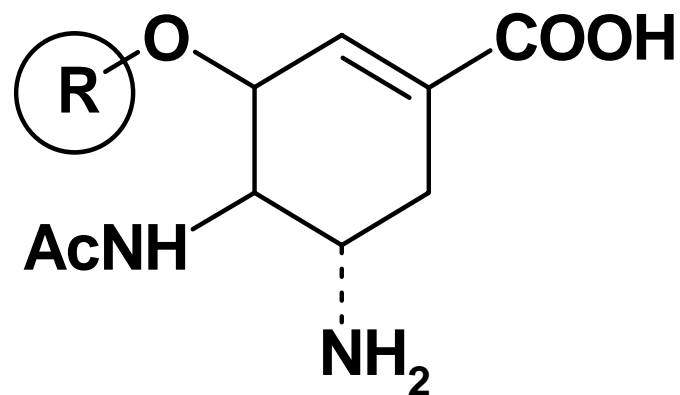


**Lead substance**



# Synthesis of homologues (2)

## Optimisation: a Medicinal Chemist's view

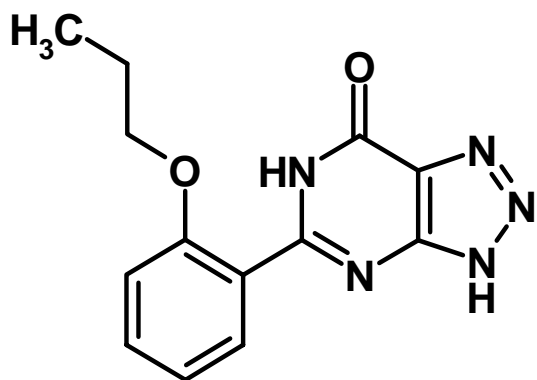


Homologation is practiced in the development of the neuraminidase inhibitor oseltamivir (Tamiflu®)

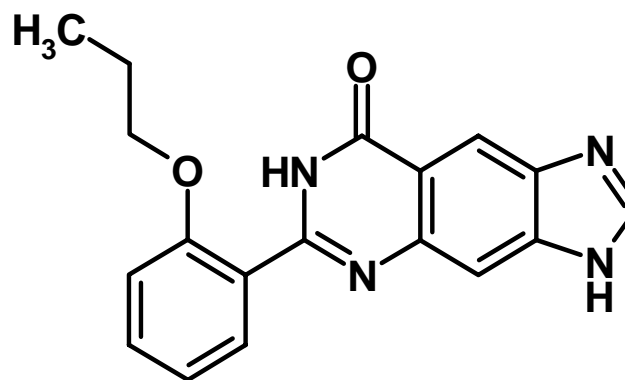
NEURAMINIDASE INHIBITION	
R =	IC <sub>50</sub> (nM)
H	6 300
CH <sub>3</sub>	3 700
CH <sub>2</sub> CH <sub>3</sub>	2 000
CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	180
CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	300
CH <sub>2</sub> CH (CH <sub>3</sub> ) <sub>2</sub>	200
CH (CH <sub>3</sub> ) CH <sub>2</sub> CH <sub>3</sub>	10
CH(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	1
CH(CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	16

Kim, C. U. et al. *J.Med.Chem.* **1998**, *41*, 2451-2460.

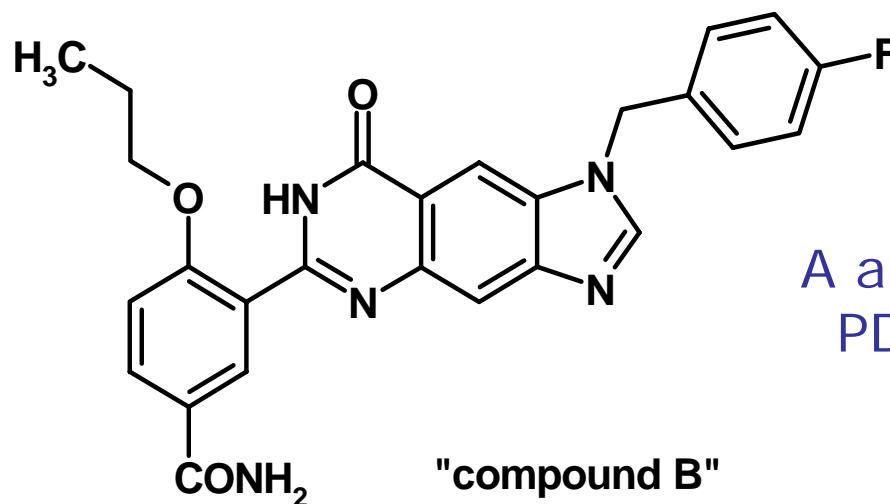
## *A successful example of benzologue design*



zaprinast



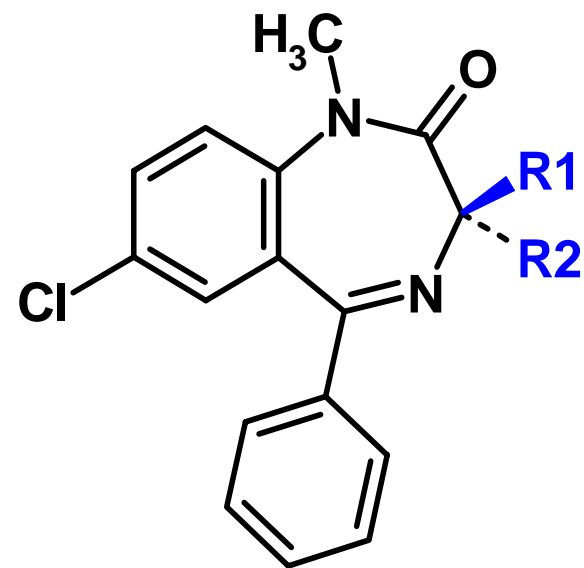
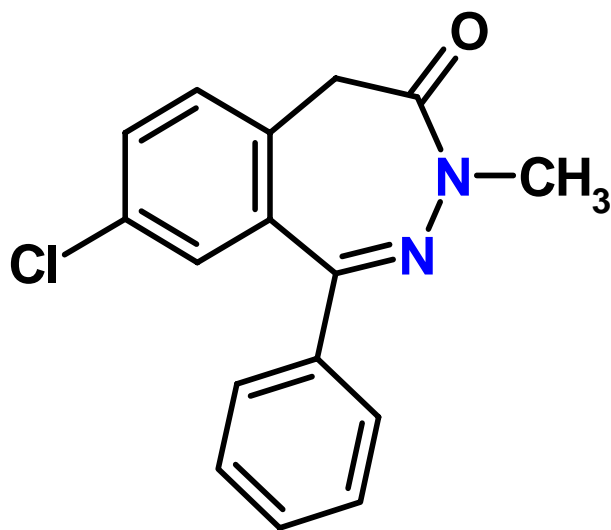
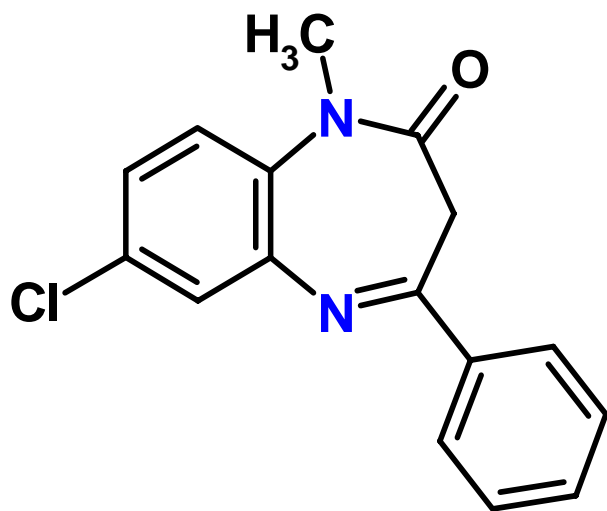
"compound A"



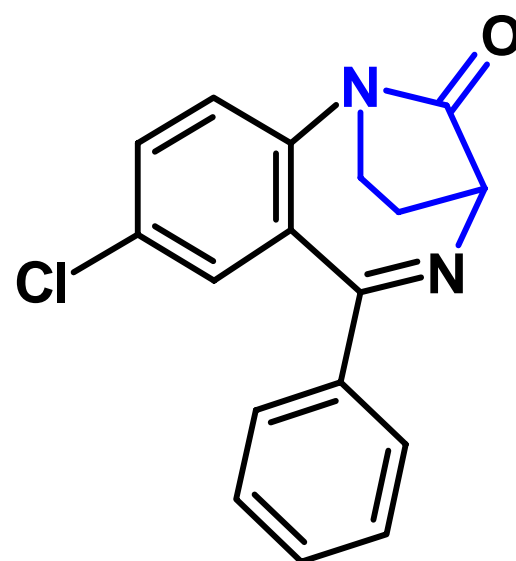
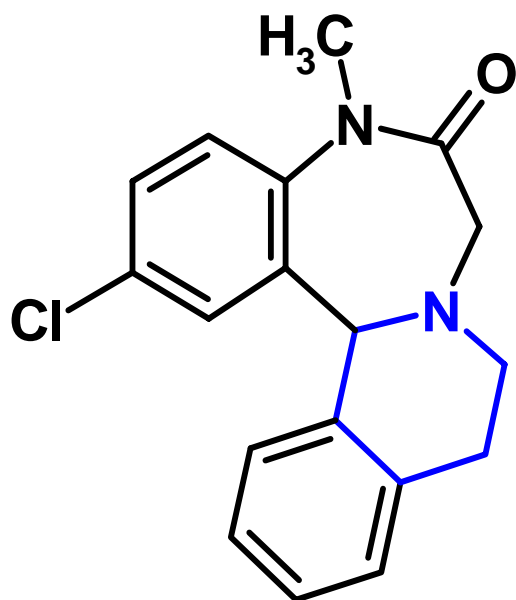
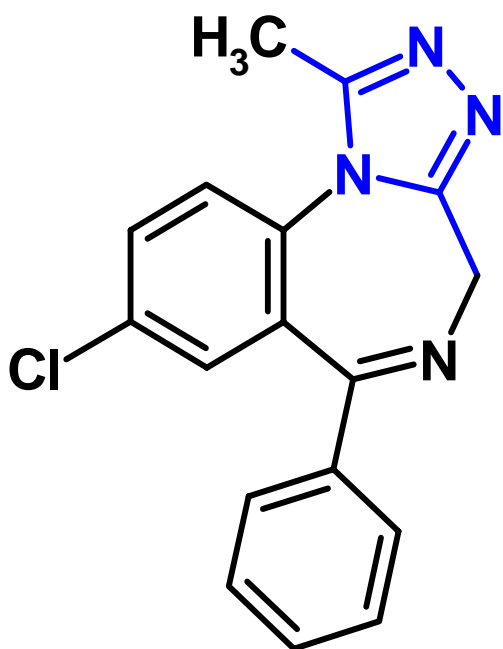
"compound B"

A and B are potent  
PDE-5 inhibitors

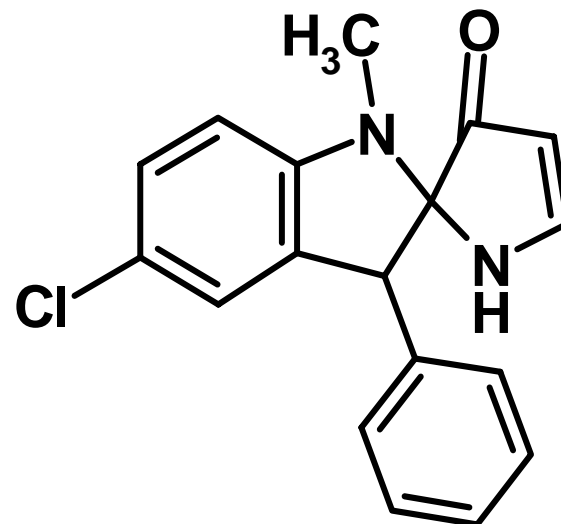
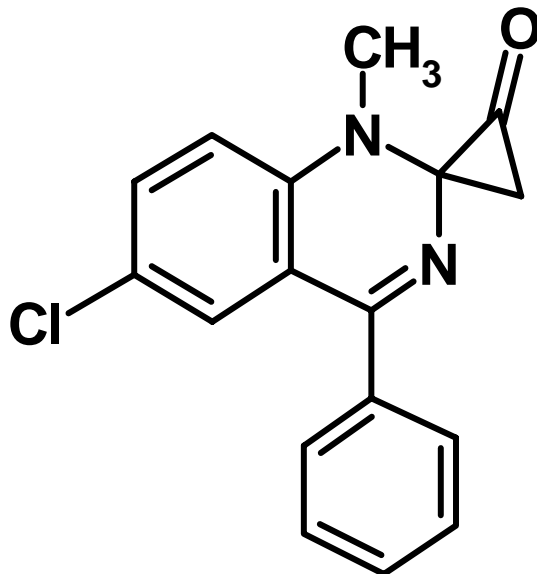
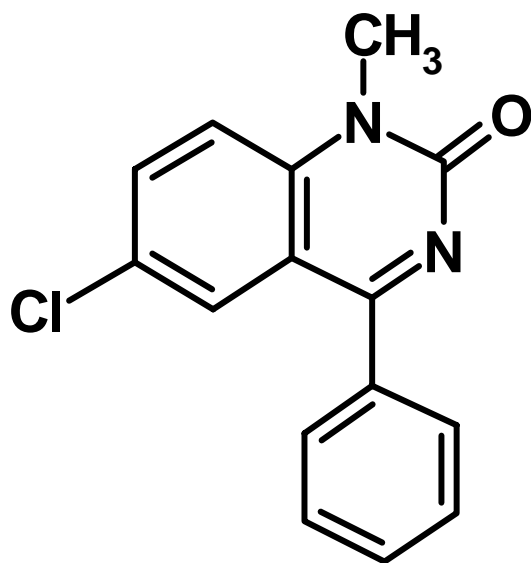
## *Synthesis of positional and optical isomers*



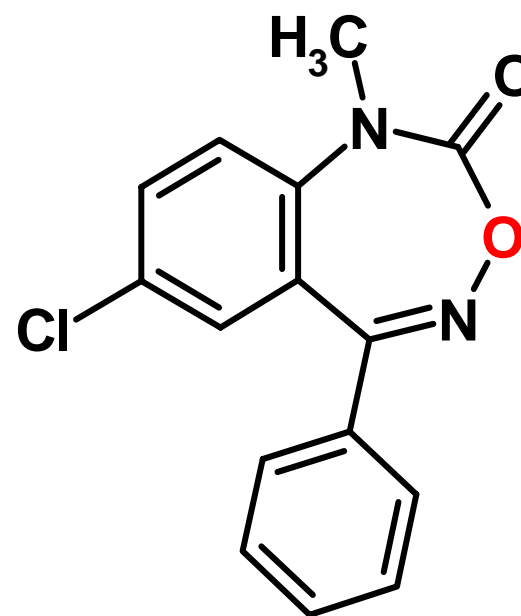
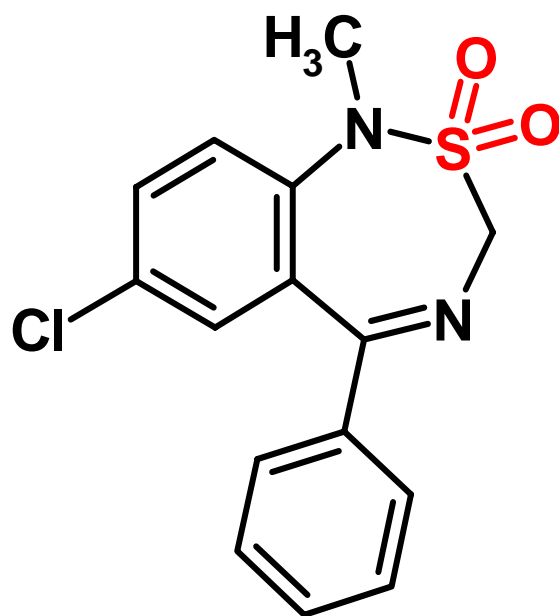
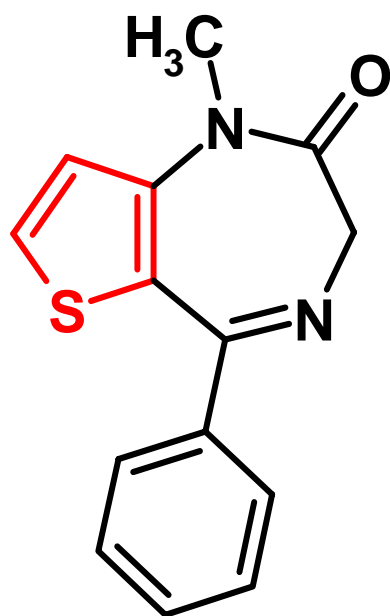
## *Ring modifications (1): additional rings and conformational restriction*



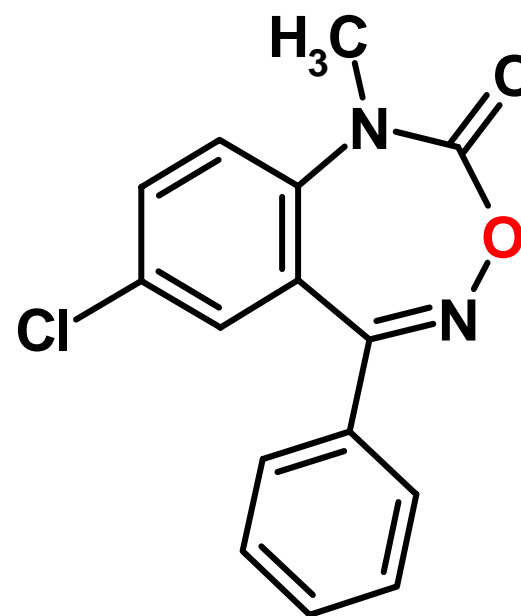
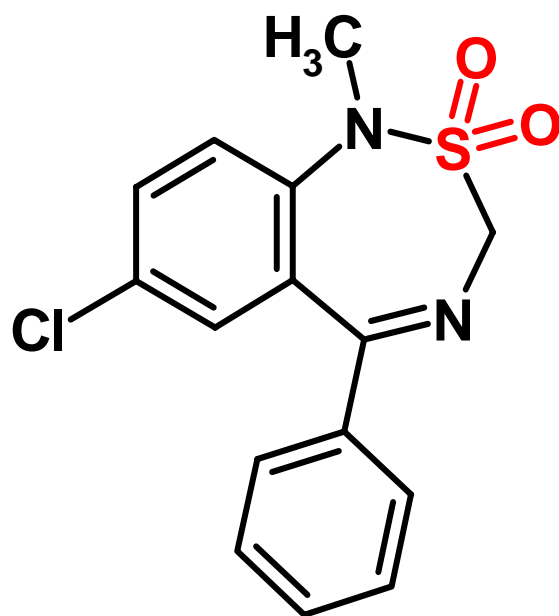
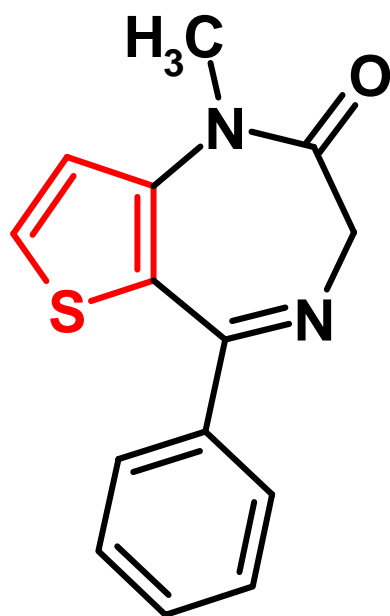
## *Ring modifications (2): ring contraction and restructured ring systems*



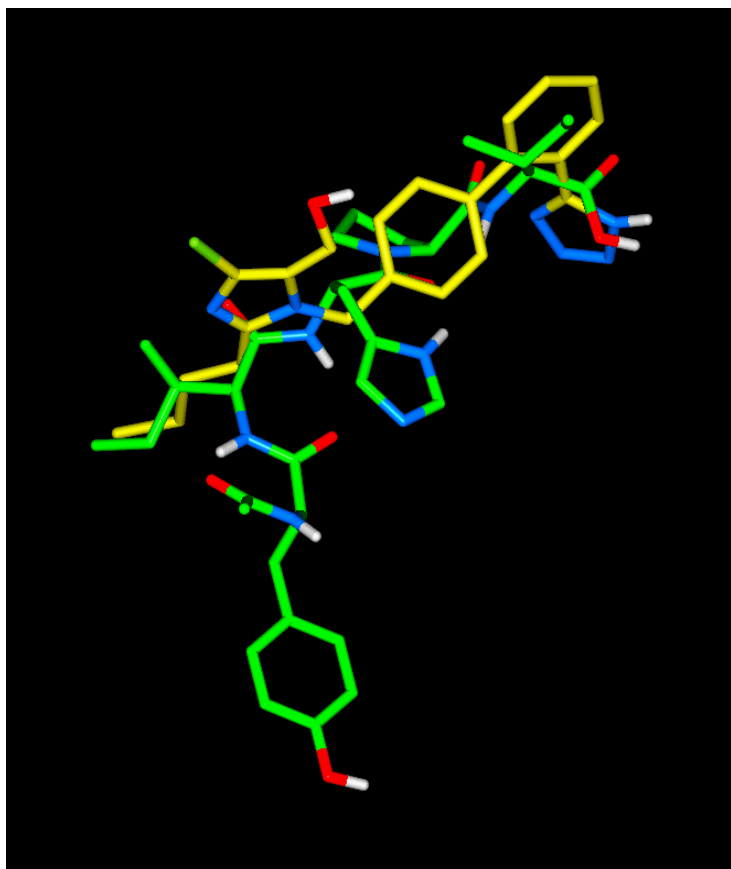
## *Isostery-bioisostery*



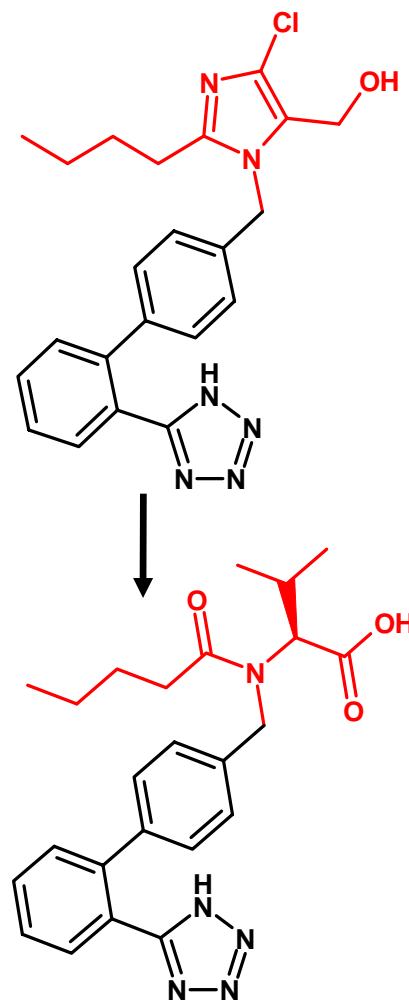
## *Isostery-bioisostery*



# Bioisostery: The Design of Valsartan



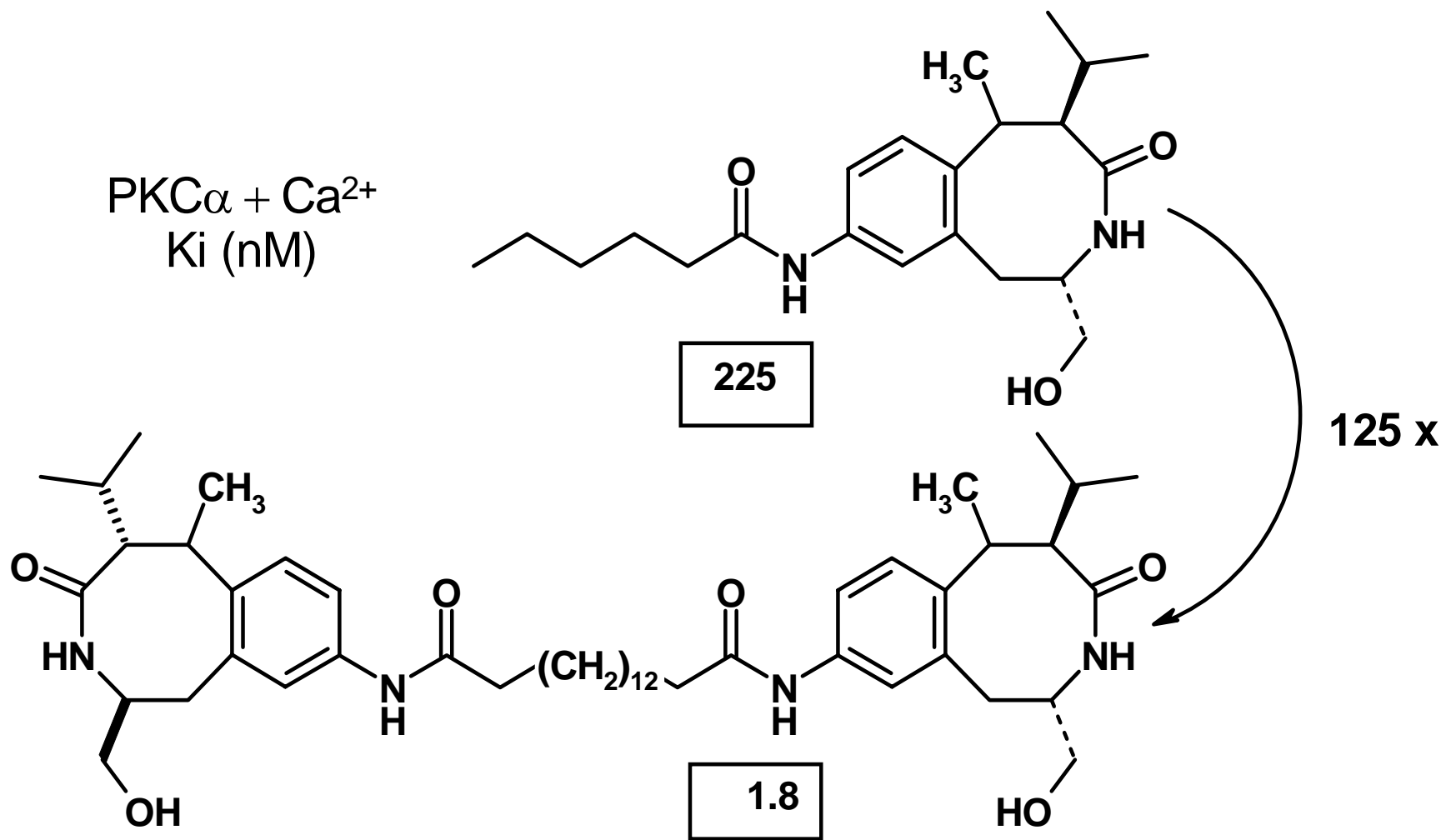
Superposition with C-terminal part of Angiotensin II



Losartan  
(Du Pont)  
 $A_{II}$  antagonist

Valsartan  
(Novartis)

## *Twin drug: Protein kinase C activators*



Sridhar et al. J. Med. Chem. **2003**, 46, 4196-4204

## *Specific aspects of CNS drugs design\**

- *Overall, compared to their non-CNS counterparts, CNS drugs tend to be more lipophilic, more rigid, have lower molecular weights, fewer hydrogen-bond donors and acceptors, fewer formal charges (especially negative charges) and lower PSA values.*

### **Thumb rules**

- If the sum of nitrogen and oxygen atoms (**N + O**) in a molecule is five or fewer, then the molecule has a high chance of permeating the BBB.
- If **ClogP - (N + O) > 0** for a molecule, then the molecule's **logBB** is likely to be positive. “logBB = log([brain/blood])”.
- The polar surface area (**PSA**) of a molecule has been shown to be a key determinant of BBB permeation. Upper limits for PSA of 60-70 Å<sup>2</sup> and 90 Å<sup>2</sup> have been suggested if good BBB permeation is to be achieved.
- Molecular weight (**MW**) should be kept **below 450 Da.**
- A **logD** value in the range 1-3 is recommended.

(\*) Clark, D.E., Ann. Rep. Med. Chem., 2005, 40, 403-415.

## *Eliminate the unwanted (1)*

Some major toxophoric groups and their bioactivation mechanisms	
<b>TOXOPHORIC GROUP</b>	<b>BIOACTIVATION MECHANISM</b>
Azo compounds,	Nitrenium ions, Tautomeric carbonium ions
Acetamides, Aromatic/Heterocyclic amines, Nitro compounds Nitroaromatic compounds	Radical formation, Oxidative stress
Bromoarenes	Arene oxide formation
Ethynyl	Ketene formation, Haem destruction
Furannes	Furanne oxide formation
Pyrroles	Pyrrole oxide
Nitrogen mustards	Aziridinium ions

## *Eliminate the unwanted (2)*

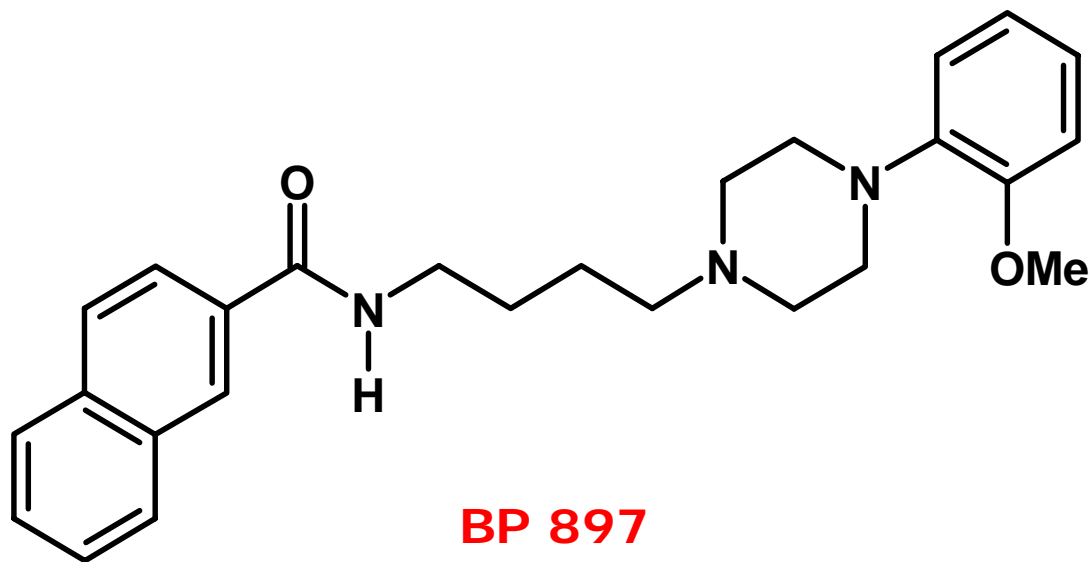
Some major toxophoric groups and their bioactivation mechanisms

<u>TOXOPHORIC GROUP</u>	<u>BIOACTIVATION MECHANISM</u>
Nitroso compounds, Hydrazines	Diazonium ions / Haem adducts / Free radical formation
Nitrosamines	Carbenium ions / DNA alkylation
Polyhalogenated compounds	Radical and carbene formation / Episulfonium with GSH
Quinones	Semiquinone radical formation / Oxidative stress / Thiol trapping
Thioamides	Thiourea formation
Thiophene	Thiophene sulfoxide formation
Vinyl	Epoxidation / Haem destruction

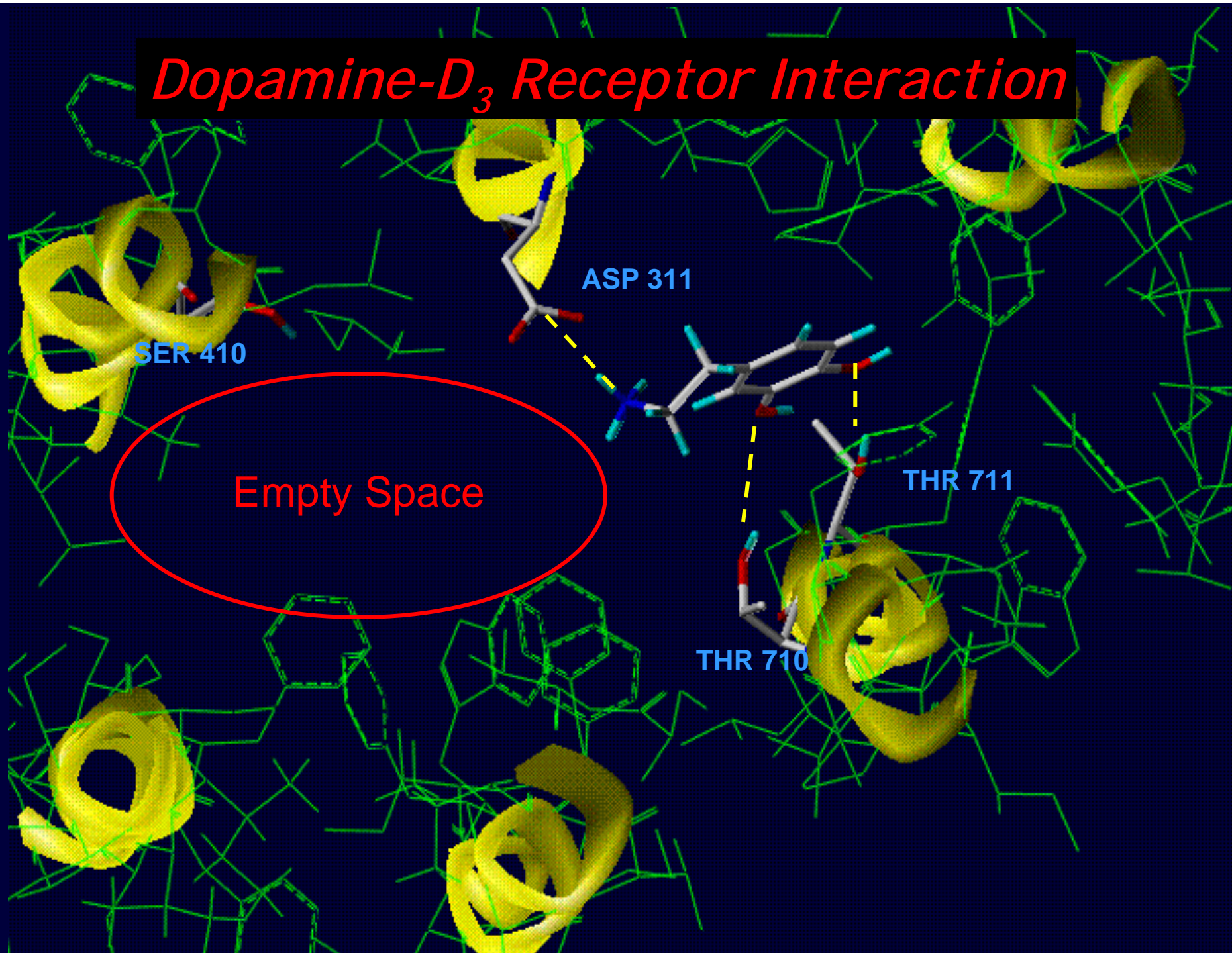


## *The Usefulness of Molecular Modeling*

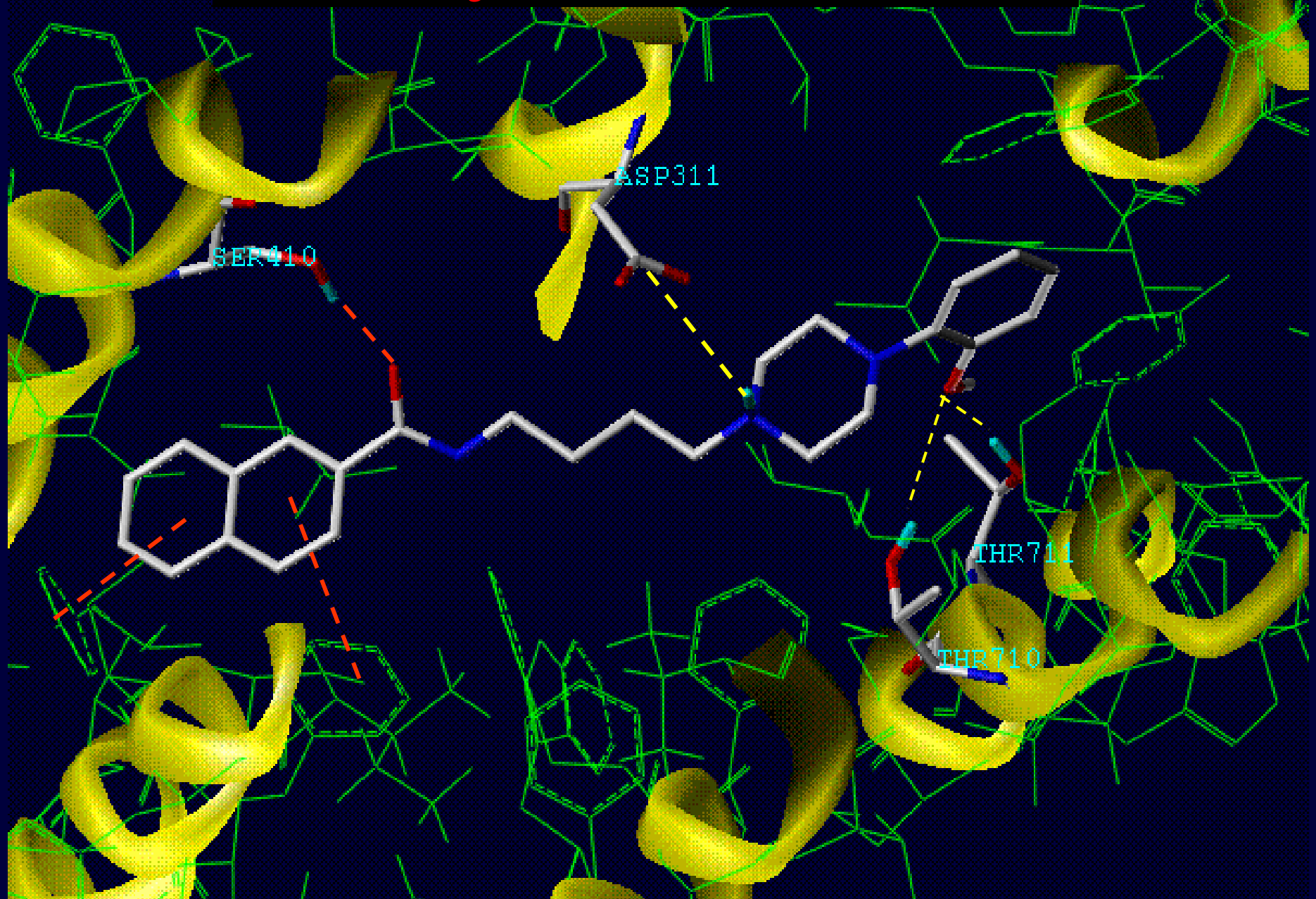
**Why does the molecule BP 897 show an almost 100 times higher affinity for the dopaminergic D3 receptors than for the dopaminergic D2 receptors?**



# *Dopamine-D<sub>3</sub> Receptor Interaction*

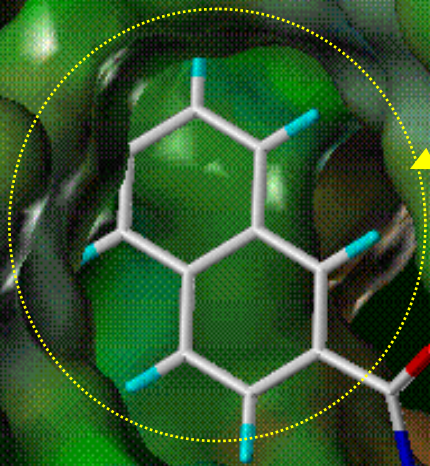


# *BP 897-D<sub>3</sub> Receptor Interaction*

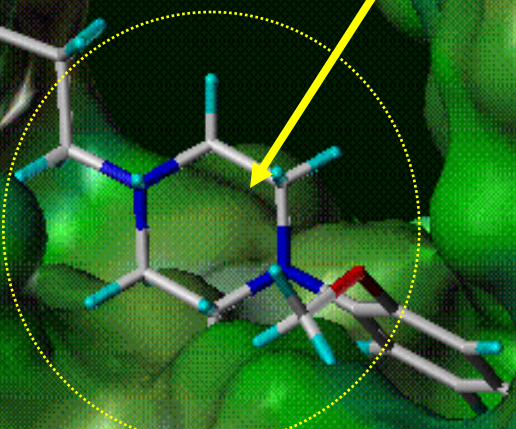


LP

Area responsible for selectivity



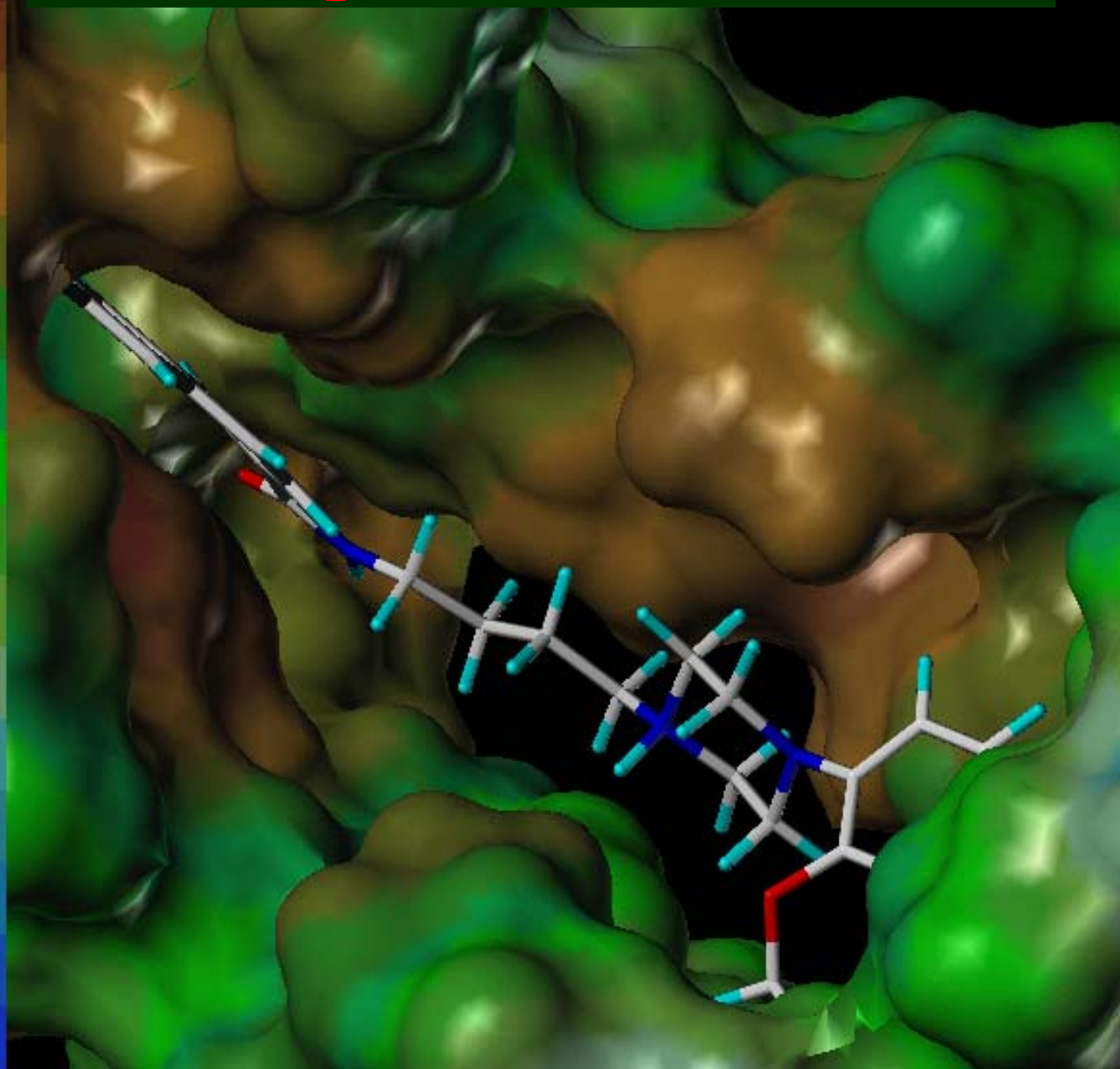
Area responsible for recognition



*Ligand- $D_3$  Receptor Interaction*

LP

# *Ligand-D<sub>2</sub> Receptor Interaction*



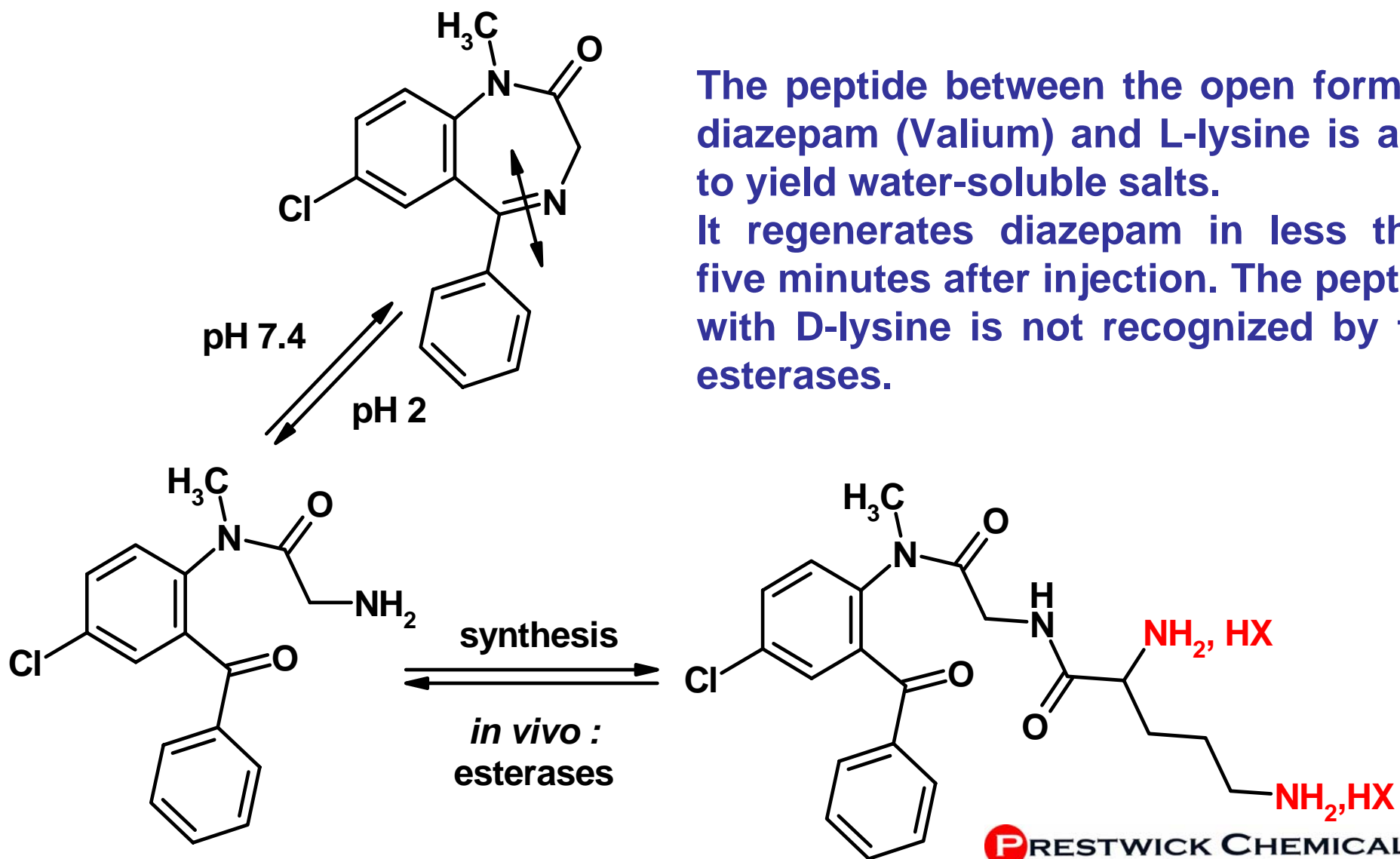
## PART 3 - CHEMICAL FORMULATION

*Objective: Transform an active molecule into a derivative suitable for the optimal administration to the patient and also allowing industrial processing.*

*It consists of correcting pharmacokinetic drawbacks: poor membrane passage, metabolic fragility, short duration of the effect etc..*

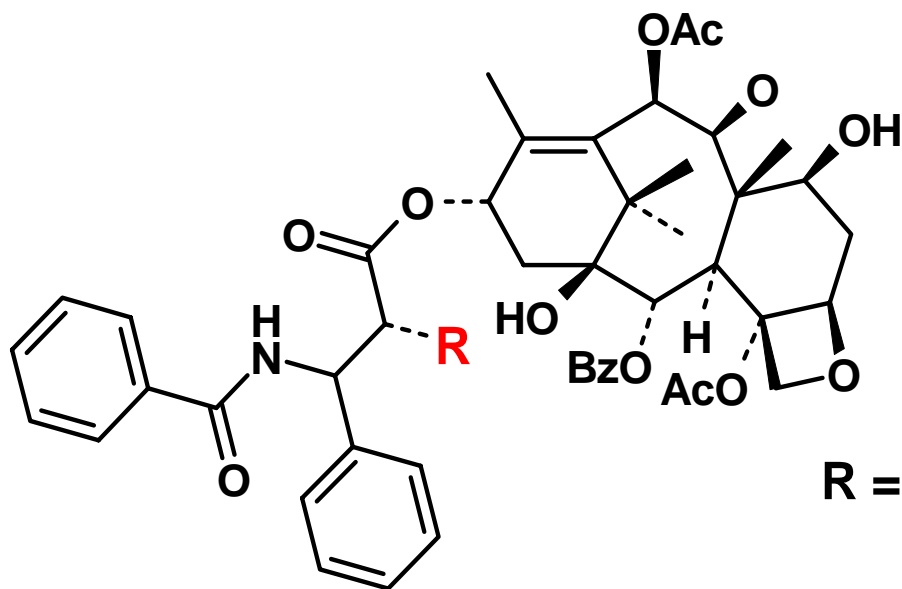
*But pure « pharmaceutical » properties can also be improved: water solubility unsatisfactory stability, hygroscopicity, polymorphism, organoleptic properties.*

## Solubilization in water

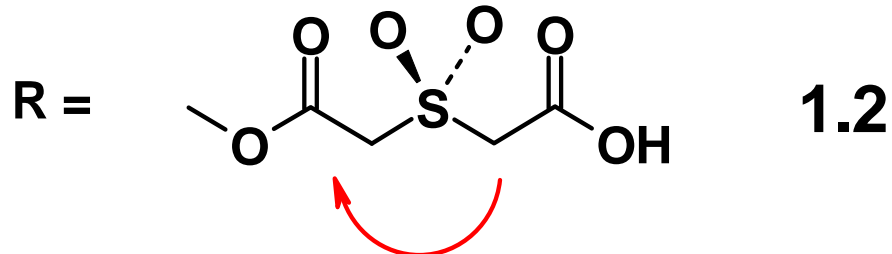
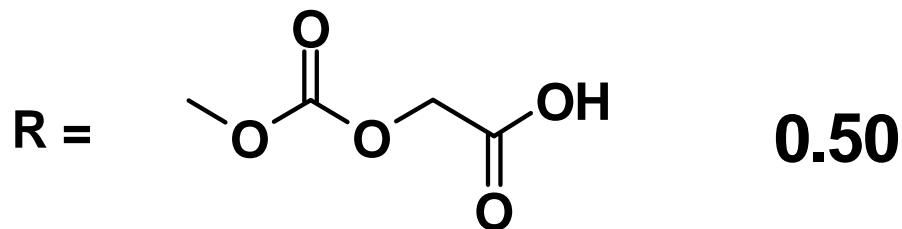


The peptide between the open form of diazepam (Valium) and L-lysine is able to yield water-soluble salts. It regenerates diazepam in less than five minutes after injection. The peptide with D-lysine is not recognized by the esterases.

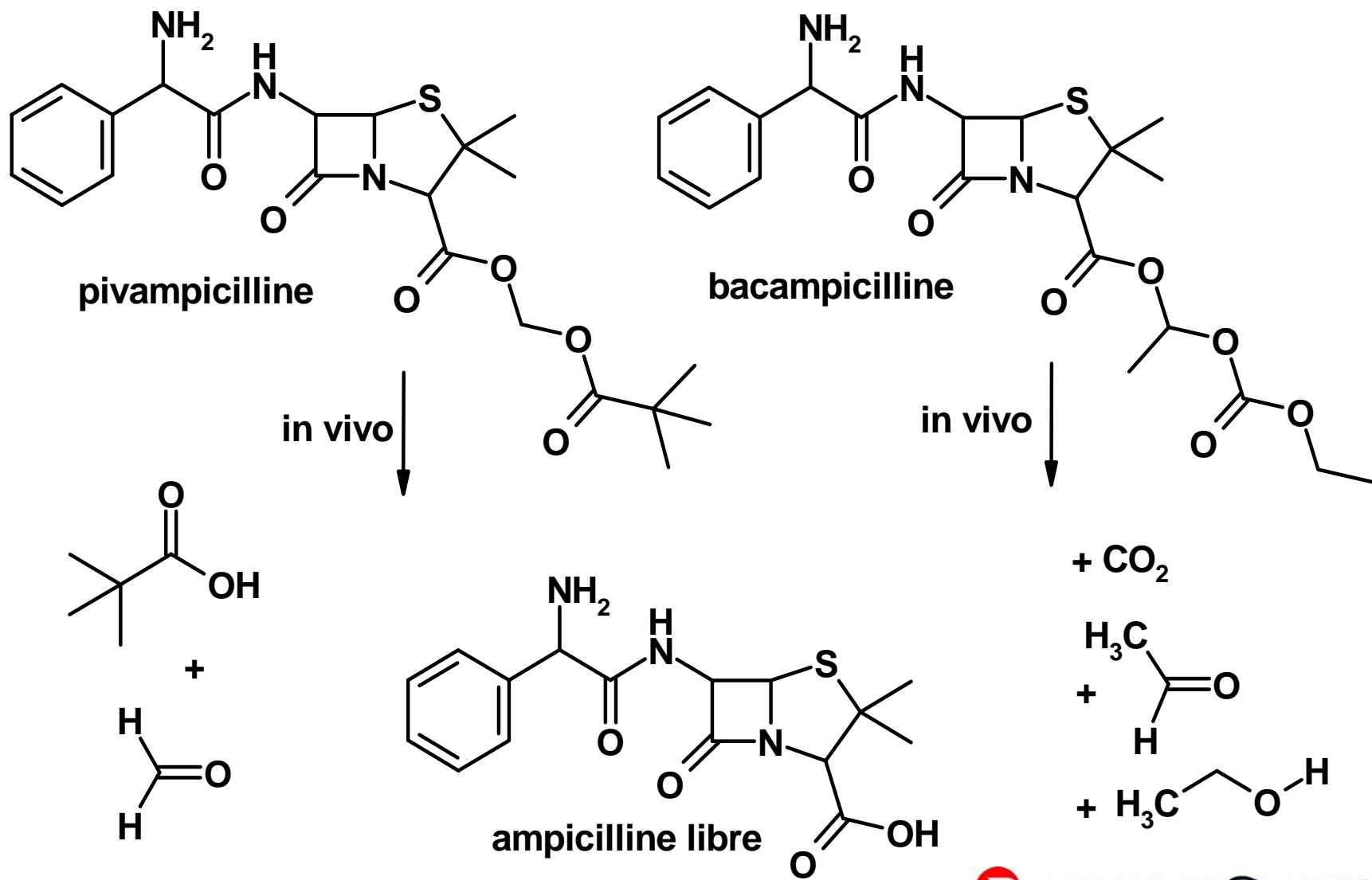
## *Solubilization in water*



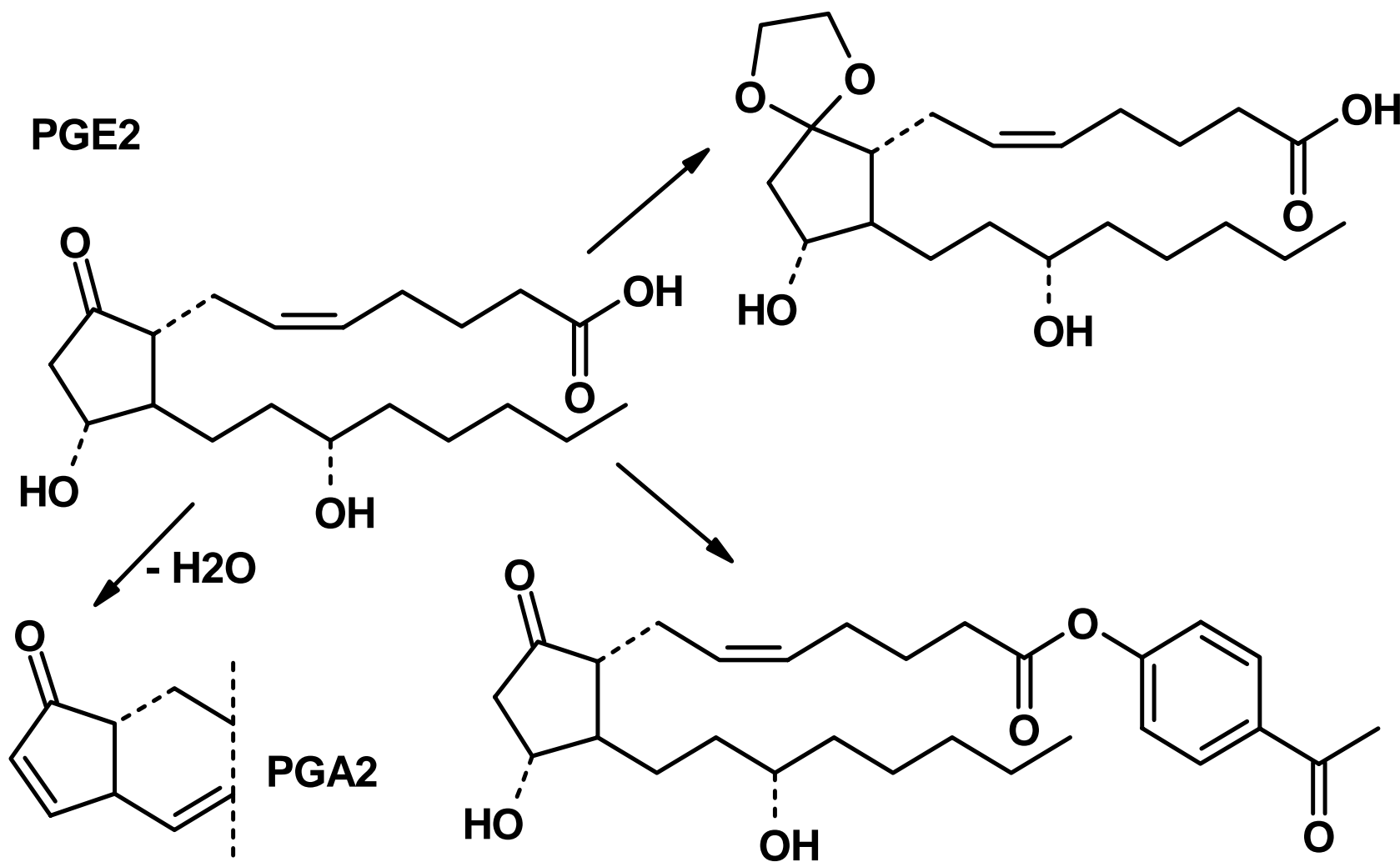
Solubility in water(mg/mL)



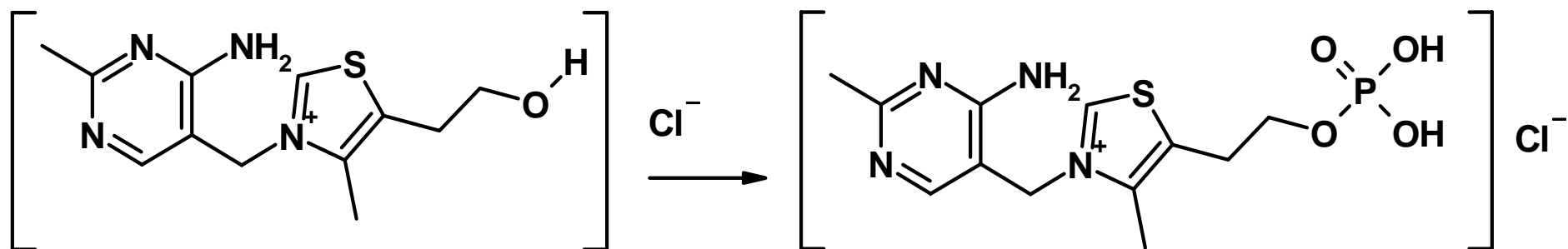
## *Facilitation of the membrane passage*



## *Increasing stability*



## Suppressing bad smell



## *Preparing the « right » salt*

- 1. It should be water-soluble**
- 2. It should not be hygroscopic**
- 3. It must correspond to thermodynamically stable polymorphic form**
- 4. The counter-anion or -cation must be non-toxic etc..**

**Anions : HCl, SO<sub>4</sub>H<sub>2</sub>, PO<sub>4</sub>H<sub>3</sub>, citric, tartaric maleic, methane-sulfonic acids**

**Cations : Na, K, Ca, Tris, Lysine, N-Methyl-glucamine**

# CONCLUSION

*During the last twenty years the pharmaceutical companies have invested massively in hit and lead **identification** technologies. Despite this effort, the productivity in terms of new therapeutic entities was low and the attrition rate was high. Most of the compounds were removed from the market for unsatisfactory ADME properties and, more recently, for toxicity reasons.*

In order to improve the production of valuable new drug molecules, and particularly CNS drugs, we recommend acting at three levels:

1. Make use of hit recognition methodologies **other than HTS** (such as feedbacks from the clinic, drug repositioning or SOSA approach) in order to design safer drugs.
2. Give more weight to the **optimization** phase, the Medicinal Chemists being adequately guided by physicochemical rules, by pharmacokinetic studies and by toxicological considerations.
3. Advantageously imply the Medicinal Chemists in the search of chemical solutions to formulation problems and thus to rescue compounds failing at the **preformulation** stage.